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Maternal Sepsis

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Abstract: Sepsis is the second leading cause of pregnancy-related mortality in the United States. Early recognition, treatment, and escalation of care for the obstetric patient affected by sepsis mitigate the risk of mortality and improve patient outcomes. In this article, we provide an overview of maternal sepsis and address topics of maternal pathophysiology, early warning signs, diagnostic criteria, early goal-directed therapy, and contemporary critical care practices. We also present an overview of common etiologies of maternal sepsis and suggested treatment approaches.
Key words: maternal sepsis, septic shock, intra-amniotic infection, endomyometritis, septic abortion

Introduction

Sepsis is the second leading cause of pregnancy-related mortality in the United States, with an estimated 14.3% of maternal deaths from 2017 to 2019 attributed to sepsis.[1,2] Despite increasing awareness, the proportion of maternal deaths from sepsis has remained stable since the 1980s.[3] As the maternal mortality rate in the United States continues to rise, preventing maternal sepsis-related deaths with prompt recognition, treatment, and escalation in care has become increasingly salient.[4,5] In response to this emerging necessity, the American College of Obstetricians and Gynecologists (ACOG) recently released a Consensus Statement via the Alliance for Innovation on Maternal Health (AIM), focusing on a consensus bundle on sepsis in obstetric care.[6]

In this chapter, we provide an overview of maternal sepsis and address topics of maternal pathophysiology, early warning signs, diagnostic criteria, early goal-directed therapy, and contemporary critical care practices. We also present an overview of common etiologies of maternal sepsis and suggested treatment approaches.

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Overview

DEFINITION OF SEPSIS

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Before 2016, sepsis consisted of multiple categories including systemic inflammatory immune response (SIRS), sepsis, and septic shock. This terminology has been abandoned in favor of sepsis and septic shock, with an emphasis on organ dysfunction rather than symptomatology. Maternal sepsis is defined by the World Health Organization (WHO) as sepsis during pregnancy, childbirth,

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postabortion, or postpartum period (up to 42 days).

PATHOPHYSIOLOGY OF SEPSIS

The pathophysiology of sepsis is a complex process driven by a dysregulated host immune response resulting in life-threatening organ dysfunction. During an infection, the host's immune system recognizes a microorganism as foreign through interactions with pattern recognition receptors. This interaction triggers an inflammatory cascade with the release of inflammatory cytokines and chemokines, as well as the activation of both the complement system and the innate and adaptive immune systems. The endothelium is also activated, resulting in 2 key responses: (1) gap junctions between the endothelial cells widen to allow the movement of plasma and inflammatory cells to the area where the infection is located, and (2) clotting factors are released, promoting the formation of systemic microthrombi preventing the spread of infection. This process is highly regulated and produces anti-inflammatory mediators, which further modulate the inflammatory response with the ultimate goal of pathogen eradication without overwhelming the host. These processes lead to the destruction of foreign pathogens as well as the production of antibodies for future immune protection.[7]

While not fully understood, there are several proposed mechanisms in which the dysregulation of the immune response to infection results in sepsis. One such proposed mechanism is that there is an overactivation of pattern recognition receptors with the consequential overproduction of both proinflammatory and anti-inflammatory mediators and an overactivation of the endothelium. This may result in spillover of mediators from the localized infection into the circulation, leading to system-wide effects and involvement of remote organs. In addition, rather than a localized production of microthrombi, there can be systemic activation of the clotting cascade with resultant disseminated intravascular coagulopathy. Finally, it is proposed that an imbalance in the sympathetic and parasympathetic nervous systems, hormones, and gene transcription may play a role in the development and progression of sepsis. It remains unknown why some organ systems are affected more than others in individual patients.[7]

Obstetric patients are at a higher risk of infection as there is a physiological downregulation of the maternal immune system. This normal downregulation of the immune system is hypothesized to confer an evolutionary advantage by protecting the developing fetus and placental growth. However, even in the postpartum period, maternal sepsis remains a critical concern. In the United States, a study examining over 66 million births showed that 50% of maternal sepsis cases occurred after discharge following admission for delivery, highlighting the need for heightened awareness in the postpartum period.[8]

SEPTIC SHOCK

Septic shock is defined as a subset of sepsis in which profound circulatory, cellular, and metabolic abnormalities are associated with a greater mortality than sepsis alone. Clinically, septic shock is identified by a vasopressor requirement to maintain a mean arterial pressure (MAP) of $\geq$ 65 mm Hg and a serum lactate $>$ 2 mmol/L despite adequate volume resuscitation.[9]

In 2016, the Third International Consensus Definitions for Sepsis and Septic Shock Task Force recommended the adoption of the terms sepsis and septic shock along with the use of the Sequential Organ Failure Assessment (SOFA) scoring system to identify organ dysfunction. An increase in the SOFA score of 2 points or more represents organ failure and is associated with an in-hospital mortality

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TABLE 1. The Sequential Organ Failure Assessment (SOFA) Score

	Score				
Organ	0	1	2	3	4
Respiratory					
PaO2/FiO2	≥ 400 mm Hg (53.3 kPa)	< 400 mm Hg (53.3 kPa)	< 300 mm Hg (40kPa)	< 200 mm Hg (26.7 kPa) with respiratory support	< 100 mm Hg (13.3 kPa) with respiratory support
Coagulation					
Platelets	≥ 150	< 150	< 100	< 50	< 20
Hepatic					
Bilirubin	< 1.2 mg/dL (20 μmol/L)	1.2-1.9 mg/dL (20-32 μmol/L)	2.0-5.9 mg/dL (33-101 μmol/L)	6.0-11.9 mg/dL (102-204 μmol/L)	> 12 mg/dL (204 μmol/L)
Cardiovascular					
MAP	≥ 70 mm Hg	< 70	Dopamine <5 μg/kg/min or any dose dobutamine	Dopamine 5.1-15 μg/kg/min or epinephrine ≤ 0.1 μg/kg/min, or norepinephrine ≤ 0.1 μg/kg/min	Dopamine > 15, or epinephrine > 0.1, or norepinephrine > 0.1
Central nervous system: Glascow Coma Score	15	13-14	10-12	6-9	< 6
Renal	Serum creatinine <1.2 mg/dL (110 μmol/L)	Serum creatinine 1.2- 1.9 mg/dL (110-170 μmol/L)	Serum creatinine 2.0-3.4 mg/dL (171-299 μmol/L)	Serum creatinine 3.5-4.9 mg/dL (300-440 μmol/L) or urine output <500 mL/d	Serum creatinine > 5.0 mg/dL (440 μmol/L) or urine output <200 mL/d

Acute increase ≥ 2 points in SOFA score indicates organ dysfunction. Reproduced with permission from Vincent et al.[10]

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greater than 10% (Table 1). A rapid way of identifying sepsis outside the intensive care unit, the quickSOFA (qSOFA), was also recommended as a means of identifying adult patients with suspected infection at higher risk of sepsis (Table 2).[9,10]

Diagnosis of maternal sepsis is challenging as many signs and symptoms of sepsis mimic several of the normal physiological changes in pregnancy, and the existing definition of sepsis does not account for these changes. For example, the SOFA score assigns 1 point for a serum creatinine >1.2 mg/dL, but this is well above the normal range in pregnancy. Similarly, a MAP <70 is considered abnormal in the SOFA but may be a normal value in the second trimester.[11] There is also potential confounding with the use of platelet count in diagnosis of sepsis as a count <150,000/mcL. While a platelet count of <150,000/mcL is abnormal in pregnancy, it can be attributed to the benign process of gestational thrombocytopenia or other pregnancy-related pathologies such as preeclampsia with severe features.[12] As such, it is imperative to maintain a high level of vigilance in the diagnosis and management of maternal infection. The Society for Maternal-Fetal Medicine recommends that clinicians have a high index of suspicion for sepsis in patients with otherwise unexplained end-organ dysfunction in the presence of active infection.[11]

OBSTETRIC SEPSIS SCORING SYSTEMS

To improve identification of patients with sepsis and those at the highest risk for morbidity and mortality, multiple scoring systems have been developed. These tools, particularly the SOFA and qSOFA, are mainstays in the rapid identification of sepsis in nonobstetric patients at greatest risk for adverse outcomes. However, these scoring systems have not yet been validated for use in the obstetric population and, as discussed, have pitfalls when used in the obstetric population.

TABLE 2. Quick Sequential Organ Failure Assessment (SOFA) Score

Quick SOFA Criteria	Points
Respiratory rate >/= 22/min	1
Change in mental status	1
Systolic blood pressure </= 100 mm Hg	1

qSOFA ≥ 2 indicates organ dysfunction. Reproduced with permission from Singer et al.[9]

In recognition of the need for an obstetric-specific early warning system, multiple pregnancy-specific scoring systems have been developed to aid in early recognition of maternal deterioration. Each of these scoring systems has limitations, and there is no preferred system, as most maternal scoring systems remain unvalidated and do not appear to outperform the nonobstetric tools.[13] These scoring systems include the Modified Early Obstetric Warning System (MEOWS), Maternal Early Warning Criteria (MEWC), and Maternal Early Warning Trigger (MEWT). MEOWS was first adopted in the United Kingdom in 2007 in response to the Saving Mothers' Lives Report which stated, "in many cases in this Report, the early warning signs of impending maternal collapse went unrecognized." The criteria utilized in MEOWS are not specific to sepsis and may lead to detection of unrecognized hemorrhage, sepsis, thromboembolism, preeclampsia, and cardiovascular complications (Table 3).[14] In the United States, the MEWC and MEWT criteria have been implemented in some hospitals. The MEWC is a simplified early warning system adapted from the MEOWS whereas the MEWT categorizes alerts into clinical pathways and provides suggested diagnostic recommendations.[15]

While the optimal tool for identifying maternal sepsis and predicting mortality remains uncertain, the AIM recommends standardization by implementation of one of the screening tools for the early identification and evaluation of obstetric patients

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TABLE 3. Modified Early Obstetric Warning System

Physiological parameter	Yellow trigger	Red trigger
Temperature; C	35-36	< 35 or > 38
Systolic BP; mm Hg	150-160 or 90-100	< 90 or > 160
Diastolic BP; mm Hg	90-100	> 100
Heart rate; beats/min	110-120 or 40-50	< 40 or > 120
Respiratory rate; breaths/min	21-30	< 10 or > 30
Oxygen saturation; %	-	< 95
Pain score	2-3	-
Neurological response	Voice	Unresponsive; pain

2 yellow or 1 red trigger(s) necessitate escalation of care and evaluation by the provider. Reproduced with permission from Singh et al.[14]

with infection and maintaining vigilance during subsequent evaluations.[6]

OBSTETRIC SEPSIS AND BASIC MANAGEMENT PRINCIPLES

In 2004, the Surviving Sepsis Campaign first outlined management principles for sepsis with the most recent revision in 2021. The underlying framework for management lies in early identification of sepsis, obtaining pertinent laboratory tests such as blood cultures and lactate levels, administration of intravenous fluids and/or vasopressors, and prompt initiation of antibiotics (Figs. 1 and 2).[16]

Early identification of sepsis and antibiotic treatment are the crux of improving outcomes for patients with sepsis. In the nonobstetric population, each hour that antibiotics are delayed reduces survival by 7.6%. Conversely, prompt initiation of antibiotics within 1 hour of diagnosis is associated with a 79.9% rate of survival to hospital discharge.[17] Though the initial studies on the golden hour of sepsis treatment excluded pregnant patients, studies have demonstrated similar outcomes in the obstetric population.[4,5]

The initial bedside assessment should include vital signs, a focused history including current or prior infections, recent exposures or procedures, any current or recent antimicrobial therapy, and a focused physical examination. If the fetus is viable, fetal monitoring should also be performed pending maternal status and whether intervention on either maternal or fetal behalf would be considered. Once the patient is stabilized, additional information and a more thorough examination can be performed.

If the patient is deemed to be unstable by either vital signs (MAP <65 mm Hg, respiratory rate > 25 breaths/minute or shortness of breath, abnormal heart rate, mental status changes, or skin color or appearance changes) or by provider assessment, rapid escalation of care should be initiated. In many institutions, this may be done via a rapid response team, but even in the absence of these teams, escalation of care should not be delayed.

Following the initial assessment, those with suspected sepsis should have a complete blood count (CBC) with differential, serum lactate, and blood cultures obtained at a minimum; additional laboratory tests that may provide additional clinical information, such as urine culture, complete metabolic panel (CMP), coagulation factors, arterial blood gas, and viral testing can also be considered. Broad-spectrum antibiotics that cover commonly implicated pathogens should be initiated with the plan to tailor treatment when a definitive diagnosis is made or causative pathogen is identified (Table 4). It is important to not delay the initiation of antibiotics for more than 1 hour if cultures cannot be collected, and cultures are still recommended after antibiotics are initiated. In patients with septic shock

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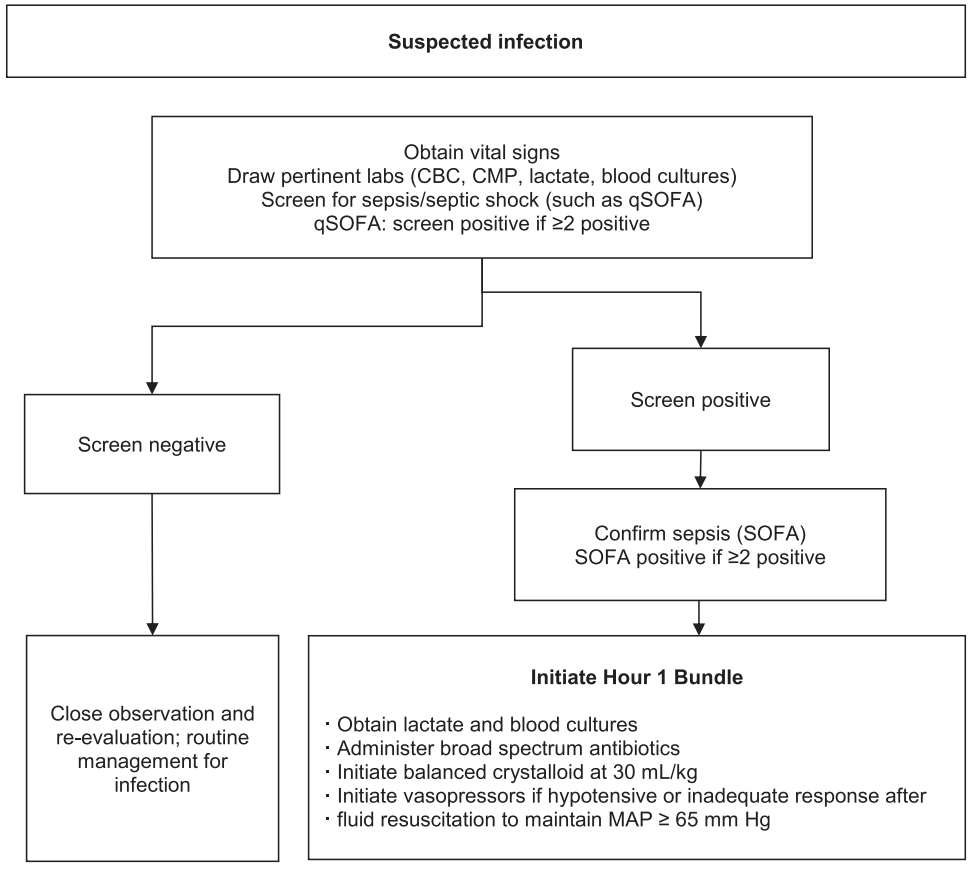
Suspected infection
Obtain vital signs
Draw pertinent labs (CBC, CMP, lactate, blood cultures)
Screen for sepsis/septic shock (such as qSOFA)
qSOFA: screen positive if ≥2 positive
Screen negative
Screen positive
Confirm sepsis (SOFA)
SOFA positive if ≥2 positive
Close observation and re-evaluation; routine management for infection
Initiate Hour 1 Bundle
· Obtain lactate and blood cultures
· Administer broad spectrum antibiotics
· Initiate balanced crystalloid at 30 mL/kg
· Initiate vasopressors if hypotensive or inadequate response after
· fluid resuscitation to maintain MAP ≥ 65 mm Hg

FIGURE 1. Algorithm for identification and initial management of suspected sepsis.

refractory to usual treatment measures, intravenous immunoglobulin administration should be considered as it may reduce overall mortality in the adult population.[18]

OBSTETRIC SEPSIS AND HEMODYNAMIC MONITORING

According to the Surviving Sepsis Campaign 2021 guidelines by the Society of Critical Care Medicine, an arterial line should be placed "as soon as practical and if resources are available."[16] Given differing local practices and resources, decisions regarding the use of invasive hemodynamic monitoring should be individualized and according to leading consensus guidelines.

OBSTETRIC SEPSIS AND FLUID RESUSCITATION

For patients with serum lactate >4 mmol/L or a MAP <65 mm Hg, fluid resuscitation should also be initiated promptly to ensure adequate tissue perfusion necessary for proper organ function. For the obstetric patient, early fluid resuscitation is further critical for the optimization of cardiac function and uteroplacental perfusion. The initial rate of infusion for nonpregnant patients with sepsis is 30 mL/kg, followed by additional fluids as clinically indicated. For pregnant patients with sepsis, it is recommended to begin with a bolus of 1 to 2 L of a balanced solution (lactated ringers) for the initial fluid resuscitation.[11] Unbalanced solutions such as normal

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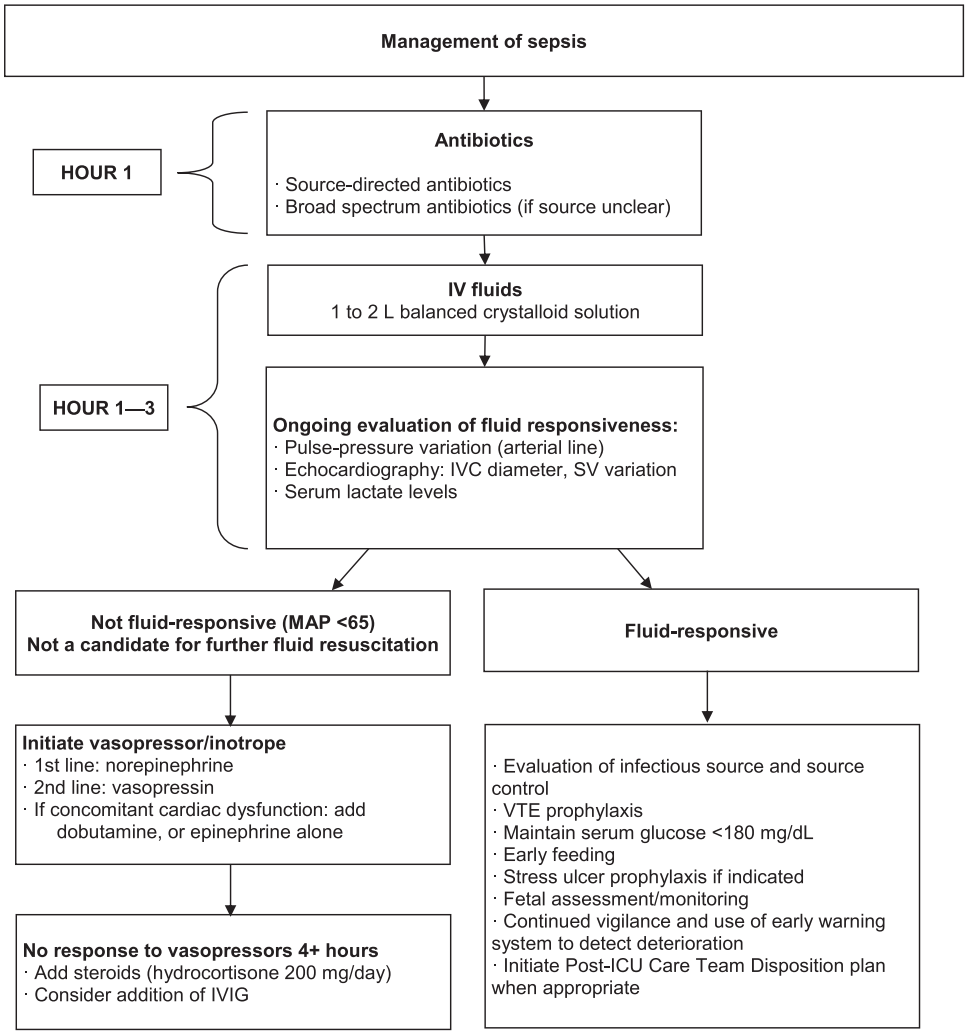
Management of sepsis
HOUR 1
Antibiotics
· Source-directed antibiotics
· Broad spectrum antibiotics (if source unclear)
HOUR 1—3
IV fluids
1 to 2 L balanced crystalloid solution
Ongoing evaluation of fluid responsiveness:
· Pulse-pressure variation (arterial line)
· Echocardiography: IVC diameter, SV variation
· Serum lactate levels
Not fluid-responsive (MAP <65)
Not a candidate for further fluid resuscitation
Fluid-responsive
Initiate vasopressor/inotrope
· 1st line: norepinephrine
· 2nd line: vasopressin
· If concomitant cardiac dysfunction: add dobutamine, or epinephrine alone
No response to vasopressors 4+ hours
· Add steroids (hydrocortisone 200 mg/day)
· Consider addition of IVIG
· Evaluation of infectious source and source control
· VTE prophylaxis
· Maintain serum glucose <180 mg/dL
· Early feeding
· Stress ulcer prophylaxis if indicated
· Fetal assessment/monitoring
· Continued vigilance and use of early warning system to detect deterioration
· Initiate Post-ICU Care Team Disposition plan when appropriate

FIGURE 2. Initial management of patient presenting with sepsis or septic shock.

saline and albumin should be avoided (except for few specific clinical situations) as they are associated with various harmful effects including renal-artery vasoconstriction, hyperchloremic metabolic acidosis, hypotension, refractory shock (not responsive to vasopressors), end-organ dysfunction, and acute kidney injury.[19–21]

Ongoing fluid resuscitation efforts should be guided by hemodynamic status and lactate clearance. While rigorous studies evaluating the utility of lactate levels in the management of maternal sepsis are lacking, available evidence suggests similar utility compared with nonpregnant patients.[22,23]

OBSTETRIC SEPSIS, SEPTIC SHOCK, AND VASOPRESSORS

Following initial fluid resuscitative efforts or at the time of diagnosis of septic shock, vasopressors should be initiated to maintain MAP $\geq$65 mm Hg.[11,16] In the obstetric population, norepinephrine is recommended as a first-line vasopressor agent, and for cases in which additional

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TABLE 4. Pathogens and Treatment of Common Obstetric and Nonobstetric Sources of Sepsis

Source	Infection	Likely causative pathogen(s)	Broad-spectrum antibiotics by suspected source
Obstetrical	Intra-amniotic infection	Polymicrobial	Ampicillin plus gentamicin A* With cesarean delivery, add clindamycin or metronidazole for anerobic coverage
	Endometritis/Septic abortion	Polymicrobial	Ampicillin, gentamicin*, and clindamycin or metronidazole. Alternative: metronidazole plus cefotaxime or ceftriaxone†
	Skin/soft tissue infection	Polymicrobial	Vancomycin plus piperacillin-tazobactam† Concern for group A *Streptococcus* or *Clostridium perfrigens*: penicillin G plus clindamycin or linezolid
	Mastitis	*S. aureus*, *S. epidermidis* Streptococci species	Dicloxacillin Vancomycin plus piperacillin-tazobactam†
Nonobstetrical	Pyelonephritis	*E. coli*, *Klebsiella*, Proteus, gram-positive organisms	Ceftriaxone Can consider monotherapy with carbapenem or piperacillin-tazobactam
	Community-acquired pneumonia	*S. pneumonia*, *K. pneumonian*, *H. influenza*, consider viral (influenza, COVID-19)	Cefotaxime, ceftriaxone, ertapenem, or ampicillin plus azithromycin, clarithromycin, or erythromycin
	Hospital-acquired pneumonia	Pseudomonas, *S. aureus*, *S. pneumonia*, *K. pneumonia*, *H. influenza*	Low-risk: ceftriazone, ampicillin-sulbactam, ertapenem, meropenem, imipenem, or cefepime. High-mortality risk: include pseudomonas (beta-lactam plus aminoglycoside or quinolone) and MRSA coverage (vancomycin or linezolid)
	Appendicitis	Polymicrobial	Antibiotic monotherapy without surgery not recommended

*Gentamycin dosed every 24 hours, ie, 5 mg/kg/d is preferred.

†With concern for Group A Streptococcus or *Clostridium perfrigens* give penicillin G plus clindamycin or linezolid.[11]

therapy is required, vasopressin is recommended as the second agent.[16] In cases where cardiac dysfunction is identified, the administration of a vasopressor that provides inotropic support, such as dobutamine or epinephrine, is recommended.[16]

SEPSIS-INDUCED CARDIOMYOPATHY

The pathophysiologic association between sepsis and cardiac dysfunction is well described in the critical care literature. In the care of patients with maternal sepsis, it is vital to maintain heightened awareness of the possibility of sepsis-induced cardiomyopathy and to consider the use of non-invasive echocardiography (transthoracic echocardiography) for evaluation. In cases that are refractory to vasopressor therapy and adequate volume resuscitation, there should be expedited efforts to investigate the possibility of cardiac dysfunction to inform further management.[24–26]

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CARE BUNDLES

The "care bundle" is a concept in which several evidence-based interventions are grouped together into a care protocol. The implementation of care bundles has shown reductions in errors and marked improvements in outcomes of critically ill patients.[27] Recently, the AIM published a consensus safety bundle on sepsis in obstetric care, providing guidance for the development of a standardized, coordinated, and multidisciplinary care program for pregnant and postpartum patients. As such, the AIM bundle provides a method for systematic evaluation and a standardized clinical practice plan that focuses on infection prevention and the early recognition and treatment of infection to prevent progression to sepsis.[6]

POST-ICU CARE

Intensive care unit admission is stressful for the patient and their loved ones. Studies have demonstrated that quality of life (QoL) is impacted after ICU admission and that patients recovering from critical illness are at risk of developing post-traumatic stress disorder.[28] Recently, there has been increasing awareness of post-intensive care syndrome (PICS), a condition that encompasses the physical, cognitive, and mental impairments that persist after ICU discharge. Survivors of critical illness, in particular those who develop PICS, are at risk of developing permanent disabilities, prolonged suffering, and consequentially a chronic and high-level utilization of health care resources.[29–31] In addition to the general PICS conditions, pregnancy-related long-term adverse outcomes may include urinary and anal incontinence, altered sexual function, and mental health conditions related to perinatal loss and/or significant neonatal morbidity. It is important to maintain awareness of these adverse QoL outcomes after obstetric ICU admission and to arrange for appropriate follow-up and support of the patient and family members.

Evaluation of nonpharmacological interventions, including early mobilization and physical rehabilitation, diaries, psychological interventions, and multidisciplinary post-ICU programs, is still in early development and research phases. While preliminary studies have described these interventions to be helpful for both physical and psychological recovery, further investigations are needed to better understand the pathologies of PICS and effective interventions that may improve patient outcomes.[32]

While there remains a paucity of high-level evidence regarding the impact of interventions in both the development and long-term outcomes of PICS, obstetric units should consider the development and implementation of a robust screening and follow-up program for critically ill peripartum patients. A standardized multidisciplinary team approach to the immediate and long-term care of critically ill patients should ideally include caregivers who were personally involved and those with specialized knowledge in all involved domains (eg, mental health, bereavement support, intensivists, and appropriate subspecialists).[33]

Once discharged from the ICU, early warning systems should be continued in the surveillance of these patients. If deterioration is diagnosed or suspected, this should be communicated in an expeditious fashion to the ICU team and/or post-ICU multidisciplinary team to ensure that these patients receive appropriate and timely treatment.

Common etiologies of maternal sepsis

Causes of maternal sepsis, obstetric and nonobstetric, often relate to the timing of infection (antepartum, peripartum, or

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postpartum). Genitourinary tract infections are the most common source of infection during the prenatal and postpartum periods, with pyelonephritis being the most common cause of nonobstetric hospitalizations during pregnancy.[34] Intrapartum sepsis is most likely to result from intra-amniotic infection, whereas endomyometritis, mastitis, gastrointestinal, and soft tissue infections are more likely to result in sepsis postpartum. Table 4 summarizes common sources, organisms, and suggested antimicrobial treatment of common sources of puerperal sepsis.

The most common pathogens implicated in maternal sepsis are *Escherichia coli,* group B streptococcus, *Staphylococcus aureus*, anaerobic bacteria, and *Listeria monocytogenes.*[34] *E. coli* is found in up to one-half of positive blood cultures in pregnant patients and is the predominant bacteria in cases of urosepsis, intra-amniotic infection, and endomyometritis.[34,35] Polymicrobial blood cultures are reported in up to 15% of cases of sepsis. However, up to two third of blood cultures and one third of all cultures of patients with sepsis will be negative with no causative pathogen identified.[36]

While less common, group A streptococcus (GAS) carries a high-mortality rate when associated with sepsis. Though the incidence of cases of GAS-related sepsis is rising globally, the incidence in the United States has remained stable at 3.48 per 100,000 persons.[37] GAS infections are characterized by rapid clinical deterioration, with 75% of infected patients having <9 hours between the first signs of infection and the development of septic shock. Twenty percent of patients with GAS die within 7 days of diagnosis due to its rapid nature and clinical severity.[37,38]

Viral and fungal infections also play a role in maternal sepsis. The most common causes of viral sepsis include influenza, varicella zoster, and herpes simplex virus; presenting symptoms are often pneumonia but may include hepatitis, encephalitis, coagulopathy, acute respiratory distress syndrome, or septic shock.[39] More recently, COVID-19 has been identified as a cause of maternal sepsis, with a mortality rate of 1.3% for severe cases.[40] Fungal infections, most commonly candida, are extremely rare in pregnancy but are associated with high-mortality rates.[36]

Obstetrical sepsis

In this section, we review pregnancy-specific causes of maternal sepsis and common microorganisms involved in these specific clinical scenarios and provide an overview of source-specific evaluations and management strategies.

SEPTIC ABORTION

Access to abortion has become increasingly restricted in the United States following the Supreme Court decision in June 2022 of *Dobbs v. Jackson Women's Health Organization*. This has translated into concern for decreased safe abortions and increased abortion and pregnancy complications.[41] It is therefore of the utmost importance that today's clinician is knowledgeable regarding the recognition and treatment of septic abortion.

Septic abortion refers to intrauterine infection occurring at $\leq$ 20 weeks gestational age. When assessing a patient for septic abortion, it is recommended that the clinician determine whether any prior uterine instrumentation has occurred as a part of their assessment. Other clinical factors that may confer an increased risk of septic abortion include prolonged uterine bleeding, retained intrauterine device, unsafe access to abortion, and retained products of conception.[42]

Upon suspicion of septic abortion, the clinician should perform a careful physical examination. The clinician should assess for abdominal rebound tenderness, perform a speculum examination, and

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carefully assess for cervical and/or vaginal trauma. In addition, a bimanual examination should be performed to assess for cervical and/or uterine tenderness to palpation. Laboratory investigations should include the following: CBC, serum lactate, blood cultures, and cervical cultures, including testing for gonorrhea and chlamydia.[42]

In addition to previously recommended goal-directed therapy, the clinician should assess for retained products of conception via ultrasonography. In patients with suspicion of a more extensive infectious process, such as pelvic infection due to uterine perforation, consideration for computed tomography scan of the pelvis and the abdomen should be given. Finally, consider Anti-D immunoglobulin administration in the Rh(D)-negative patient.[42] In the septic patient with evidence of retained products of conception, following initiation of early goal-directed therapy of intravenous fluids and antibiotics, uterine aspiration is recommended for source control independent of fetal cardiac activity.[43]

Causative bacteria in the case of septic abortion generally arise from the vaginal flora; however, anaerobes should also be considered, especially in patients presenting with sepsis with shock.[42] While most cases of septic abortion are thought to be polymicrobial, patients with GAS infections are at risk for toxic shock syndrome. In patients where GAS infection is suspected, the addition of clindamycin to high-dose penicillin is recommended to reduce the release of GAS virulence factors.[44] When clindamycin cannot be administered, linezolid is an appropriate alternative antibiotic for the treatment of GAS infection.[45]

INTRA-AMNIOTIC INFECTION

Clinical intra-amniotic infection affects 4% of births and is the most common obstetric etiology of peripartum infection worldwide.[46] Intra-amniotic infection (IAI), previously termed chorioamnionitis, refers to infection involving the amniotic fluid, fetus, umbilical cord, and membranes. In 2015, the National Institute of Child Health and Human Development (NICHD) recommended the terminology "intra-amniotic infection" to standardize the diagnostic criteria for intrauterine infection, delineating maternal fever from suspected and confirmed IAI.[47] The ACOG endorses the NICHD criteria with the exception that presumptive diagnosis of IAI should be made in patients with isolated fever ≥ 39C (102.2F) without another clear source, as these patients are at high risk of adverse infectious outcomes.[48]

In patients with a diagnosis of IAI, it is crucial to maintain vigilance for the development of sepsis. Obstetric literature has described an up to 8- to 12-fold increased odds for sepsis, with approximately 12% to 20% of maternal sepsis preceded by IAI.[13,49] As such, broad-spectrum parental antibiotics should be administered promptly at the diagnosis of IAI to treat maternal and fetal infection, reduce neonatal risk of infection, and reduce maternal and neonatal consequential infectious morbidities.[50]

IAI is typically a polymicrobial infection involving enteric or lower genital tract flora which migrate to the decidual-chorionic interface with eventual passage into the amniotic cavity. Membrane rupture is not necessary for infection of the amniotic cavity as maternal bacteremia may also develop should microorganism(s) access the placental intervillous space resulting in transplacental infection of the fetus. The eventual development of infection is influenced by a complex interaction of local host factors and defense mechanisms, as well as the virulence of the pathogenic organism(s).[51]

Basic management principles, as previously described, should guide the initial assessment, with focus on maintaining a with high index of suspicion for IAI and

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the development of sepsis. Blood cultures and serum lactic acid are indicated for patients with suspected maternal sepsis secondary to IAI. In addition to prompt administration of broad-spectrum antibiotics (Table 4), patients with IAI should be delivered regardless of gestational age. Labor should be managed vigilantly, and appropriate progression should be ensured. Intra-amniotic infection alone is not an indication of immediate cesarean delivery.[48] Nonetheless, the prudent clinician should consider expediting delivery for maternal benefit in certain clinical scenarios (eg, when remote from delivery and/or there is decompensation of maternal status). In these challenging clinical circumstances, there should be thoughtful and individualized consideration of the benefits of proceeding with cesarean delivery versus the fact that for patients with IAI receiving antibiotics, the duration of labor is not correlated with adverse neonatal outcomes, and that cesarean delivery would confer increased surgery-associated risks including wound infection, intra-abdominal abscess, endomyometritis, and thrombotic complications.[52,53]

The optimal duration for postpartum parenteral antibiotic therapy in the absence of maternal sepsis has not been determined conclusively, and there is no evidence that oral antibiotics are beneficial after discontinuation of parenteral therapy. Some experts provide a single additional dose or 24-hour course of parental antibiotics in the postpartum period following cesarean delivery, given the increased risk of infectious morbidity in patients with IAI after cesarean delivery.[48] Regardless of the delivery route, it is reasonable to continue antibiotics following delivery when there are any concerns or suggestive signs or symptoms of sepsis at any time during the intrapartum or immediate postpartum course.

ENDOMYOMETRITIS

Postpartum endomyometritis, defined as an infection of the decidua or myometrium, occurs in 1% to 3% vaginal births and up to 27% of cesarean deliveries.[54] Endomyometritis is typically polymicrobial, involving both aerobic and anaerobic bacteria from the lower genital tract. Similar to the pathogenic mechanism of IAI, endomyometritis is likely due to the migration of endogenous lower genital tract flora into the uterine cavity during labor and birth, with the subsequent development of infection relating to a complex interaction of local factors, host defense mechanisms, and virulence.[55]

Postpartum endomyometritis is a clinical diagnosis of infection and one or more of the following presenting signs/symptoms: uterine tenderness, abnormal vaginal discharge or odor, and delay in rate of reduction of the uterus. Laboratory evidence (ie, elevated white blood cell count or serum lactate) is often used to support the diagnosis or monitor for progression of infection. Blood, wound, and/or uterine cultures and sensitivities are useful for directing antibiotic treatment regimens.[37] In the critically ill patient with postpartum endomyometritis, there should also be consideration of obtaining imaging studies such as pelvic ultrasonogram or CT imaging to evaluate for alternative diagnoses such as retained products of conception, pelvic abscess, or septic pelvic thrombophlebitis.[56]

The clinical course of endomyometritis can be complicated by peritonitis, intra-abdominal abscess, postpartum hemorrhage, or sepsis in up to 4% of patients.[54] Again, application of basic management principles of maternal sepsis and septic shock (Figs. 1 and 2) and expedited administration of broad-spectrum antibiotics at diagnosis (Table 4) is paramount for optimal patient outcomes. In addition, for the critically ill patient with postpartum endomyometritis, it is imperative to consider less common causative etiologies of infection as prompt diagnosis and directed treatment(s) will optimize patient outcomes. For example, uncommonly,

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endomyometritis may be due to genital mycoplasmas and sexually transmitted organisms such at *Chlamydia trachomatis*. For immunocompromised patients, such as those living with HIV, other less likely pathogens such as herpes simplex virus and cytomegalovirus may be implicated.[57–59] Finally, GAS should be considered as a possible etiology for critically ill postpartum patients presenting with septic shock, necrotizing fasciitis, or toxic shock syndrome. Invasive GAS infection is catastrophic and has been associated with over half of mortality cases among obstetric patients with sepsis.[60,61] Owing to the significant morbidity and mortality of invasive GAS, optimal outcomes are achieved with vigilant awareness and early antibiotic treatment based on presumed diagnosis (Table 4).

Early surgical consultation for consideration of surgical intervention to obtain source control should be obtained. This is especially important in patients who have signs of septic shock, have findings concerning for GAS or necrotizing fasciitis, are unresponsive to medical management, or are decompensating despite interventions. Surgical intervention may include abdominal exploration as well as hysterectomy.

PERINEAL WOUND INFECTION

Vaginal lacerations are common at the time of delivery with 53–79% of patients experiencing any type of vaginal laceration.[62,63] The incidence of obstetric anal sphincter injuries (OASIS) is thought to be as high as 11% with vaginal delivery in nulliparous patients and confers a significant infectious risk.[64] One randomized control trial demonstrated a decreased rate of postpartum wound complications 2 weeks postdelivery in patients receiving a single dose of a second generation cephalosporin compared with placebo (8% vs. 24%, $P = 0.04$).[65] ACOG considers it reasonable to administer a single dose of antibiotic at the time of repair of an obstetric anal sphincter injury.[66]

Close postpartum surveillance for wound breakdown of OASIS is necessary due to the high rate of postrepair complications of OASIS tears. One systematic review, including data from the United States, the United Kingdom, and Denmark, reported the rate of wound breakdown in OASIS to be as high as 25% and wound infection 20%.[67] Patients who present with signs of sepsis following vaginal delivery with or without obstetric anal sphincter repair should have a careful pelvic examination to assess for wound infection or breakdown and, albeit rare, sponge retention.

Prompt recognition of sepsis secondary to perineal wound infection is essential for optimization of outcomes in patients with deep infections or necrotizing fasciitis. The first step in management of sepsis secondary to perineal wound infection remains early goal-directed therapy (Figs. 1, 2) with carefully selected broad-spectrum antibiotics covering common flora of the genitourinary and gastrointestinal systems (Table 4). In addition, consideration should be given to the need for surgical exploration and debridement to obtain source control. Urgent surgical intervention is imperative in cases of sepsis secondary to necrotizing fasciitis as early debridement is associated with a decrease in patient mortality.[68,69]

MASTITIS

Lactational mastitis is a relatively common postpartum diagnosis. Fortunately sepsis secondary to lactational mastitis appears to be a rare occurrence as there are few case reports in the literature for patients hospitalized for sepsis secondary to lactational mastitis.[70,71]

Patients presenting with sepsis secondary to lactational mastitis will likely have breast-specific complaints such as erythema and breast pain. We recommend a thorough examination of the breasts with careful inspection for breast abscesses. Early goal-directed therapy should be

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initiated first followed by prompt incision and drainage for source control when an abscess is present. When an abscess is present, wound cultures should also collected to allow for tailored antibiotics once speciated. Furthermore, continued breastfeeding or pumping is recommended in the affected patient as cessation of breastfeeding can result in milk stasis, thus conferring further infectious risk.[72]

Nonobstetrical sepsis

When caring for patients affected by sepsis, the obstetrician should also consider nonobstetrical sources of sepsis. The most common nonobstetrical source of sepsis in the antepartum patient is pyelonephritis. Other common sources include respiratory and gastrointestinal sources such as pneumonia and appendicitis.[11] Early goal-directed therapy with prompt administration of antibiotics is essential in patients with nonobstetrical sources, given the increased morbidity of these infections in pregnancy. Table 4 highlights suggested antibiotic regimens for respective suspected sources of sepsis. Appropriate consultation of other specialties should also be considered for nonobstetric etiologies of sepsis, such as general surgery in cases of appendicitis or cholangitis or urology in cases of infected nephrolithiasis.

Summary

As the maternal mortality rate rises in the United States, with a high proportion of these deaths due to sepsis, it has become increasingly critical for the contemporary obstetrician to have a competent grasp of current recommendations surrounding recognition and treatment of maternal sepsis. To that end, we hope that the tools reviewed in this article are useful to the practicing clinician.

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